REMARKS

Claims 1-17 are pending. Claims 18-32 were withdrawn pursuant to restriction and have been cancelled in this amendment. Claims 1-17 are amended to address minor issues of clarity and form and no new matter is introduced by the amendments. The amended claims are fully supported by the specification and claims as originally filed.

The pending claims were rejected for alleged lack of unity, alleged indefiniteness, alleged lack of written description, alleged anticipation and alleged obviousness. Claims 4, 5 and 17 were also objected to for a variety of informalities. Applicants traverse all objections and rejections of record for the reasons noted herein.

CLAIM OBJECTIONS

Claim 4 was objected to for inclusion of a stray underline of the period at the end of the claim. This has been corrected by amendment as helpfully suggested by the Examiner. Accordingly, the objection should be withdrawn.

Claim 5 was objected to for failure to include a period at the end of the claim. This has been corrected by amendment as helpfully suggested by the Examiner. Accordingly, the objections should be withdrawn.

Claim 17 was rejected for allegedly being of improper dependent form, for alleged failure to further limit the claimed composition. The claim has been amended to recite a property of the claimed composition of claim 17 (expressibility of the shRNA in an animal cell). Accordingly, claim 17 is now in proper dependent form and the objection must be withdrawn.

To expedite prosecution, claims 1-17 are also variously amended to address issues of grammar, to provide for use of approved Markush claim format and to address other minor formalities.

THE CLAIMS ARE DEFINITE

Claims 3-6 were rejected for allegedly failing to clearly identify which numbered nucleotides were being referred to. The claims have been amended to specify that the relevant sequence is SEQ ID NO:21, which corresponds to Genbank Accession

number X00588. The specification has been amended to add reference to SEQ ID NO:21, in reference to Genbank Accession number X00588, and the corresponding sequence has been added to the sequence listing. Accordingly, as there is now no possibility of confusion regarding which sequence is at issue in the claims, the rejection must be withdrawn.

THE CLAIMS ARE NOVEL OVER TALKE ET AL (US 5,891,689)

Claims 1, 7, 16 and 17 were rejected for alleged anticipation by Talke et al. (US 5,891,689). Applicants traverse.

Talke et al. fail to describe several features of the rejected claims.

First, Talke et al. do not teach a gene that encodes an shRNA.

With respect to this element of the claims, the rejection argues that the claim does not require that the gene encode an shRNA, only that it comprise sufficient genetic information to encode the shRNA. The rejection also alleges that the genes of Talke are "reasonably considered to read" on such a gene. Action page 10. No citation of a gene described by Talke that actually encodes an shRNA (or even that contains information to encode such an RNA) is provided in the Action. Indeed, no such gene exists in the cited reference. Applicants note that the claims have been amended to require that the relevant gene encode an shRNA. Nowhere in Talke is such a gene described. No gene described by Talke et al. encodes an shRNA. Indeed, the technology at issue in Talke relates to entirely different types of genes (e.g., genes encoding ribozymes). Thus, Talke et al. simply fail to recite this element of the claims.

Second, Talke fails to provide "a plurality of receptor targeting agents that are capable of targeting a receptor."

Talke relates to microparticles that are targeted using heme. Heme is a small organic molecule that is a degradation product of hemoglobin. Although Talke hypothesizes that there is a heme receptor, no such receptor has actually been identified. See, e.g., Uc et al. (2004), attached. Indeed, the available evidence suggests that heme uptake is *not* actually mediated by a receptor. See Light and Olson (1990), attached. Talke et al. provide no evidence of saturation or other evidence of receptor mediated

uptake of heme-conjugated molecules. Thus, there is no "targeting agent that targets a receptor" in the technology described by Talke et al.

These structural differences between Applicants' claimed composition and the Talke et al. microparticles also leads to vastly different properties of the respective compositions. Compositions of the invention have been shown to be active in vivo, targetable in vivo, to inhibit gene expression in vivo via RNAi and even to increase cancer survival. No Talke composition has any of these properties. For example, Talke et al. provide no evidence of the expression of any gene with their microparticles, either in tissue culture or in living animals. No composition of Talke et al. is shown to express a gene in a living animal, or to be targetable in vivo, or to induce RNA interference via the expression in vivo of a targeted shRNA. Indeed, Talke et al. provides no discussion as to how the Talke microparticles are structurally configured to be transcytosed across microvascular barriers in vivo. With reference to targeting, Talke only refers to targeting the liver, which has no microvascular barrier to microparticles 100-200 nm in size. Accordingly, the structure of the Talke compositions are entirely distinct from those of the present invention, the properties of the compositions are entirely different and the way in which the compositions are useful are entirely different. Indeed, the Talke et al. reference is essentially unrelated to the present invention. The rejection must be withdrawn.

ZHANG (2003) IS NOT A PUBLICATION BY ANOTHER

Claims 1 and 7-17 were rejected for alleged anticipation by Yun Zhang, Ruben J. Boado, and William M. Pardridge (2003) "In vivo knockdown of gene expression in brain cancer with intravenous RNAi in adult rats" The Journal of Gene Medicine 5:1039-1045 (Zhang et al., 2003). Applicants traverse.

As evidenced by the attached "Katz" style declaration (*see, In re Katz* 215 USPQ 14 (CCPA 1982)), Zhang et al. 2003 is not a publication by another as required by 35 USC § 102(a). That is, as specified, e.g., by MPEP 715.01(c), a 35 USC § 102(a) reference can be overcome by providing a declaration pursuant to 37 § CFR 1.132, stating that co-author Applicants on a 35 USC § 102(a)-style reference are the actual inventors of the claimed subject matter. Such a declaration is provided herewith. The

declaration establishes that, to the extent the reference teaches Applicants' claimed invention, the relevant reference is a publication of Applicants' own invention and, therefore, cannot present a statutory bar under 35 USC § 102(a). Accordingly, all rejections that rely on Zhang (2003) must be withdrawn.

THE CLAIMS ARE NOVEL OVER MCSWIGGEN ET AL.

Claims 1-13 and 15-17 were rejected for alleged anticipation by McSwiggen et al. (US 20004/0192626A1). Applicants traverse.

The rejection acknowledges that several of the claimed features of the invention are not expressly taught by McSwiggen et al., but, nevertheless, argues that the features are "inherent" in the compositions proposed by McSwiggen et al. Action at page 13.

In fact, the compositions of the invention are simply not taught at all, expressly or inherently, by McSwiggen et al. There is simply no passage in the McSwiggen article that relates to a composition that has a gene encoding an shRNA inside of a liposome that has targeting agents conjugated to it by conjugation agents.

The passage supposed in the rejection be most relevant to this basic composition is found at paragraphs 0565-0572. At most, in this section of the document, McSwiggen et al. propose a laundry list of possible delivery methods for siRNA. These include cationic liposomes and immuno-liposomes (specifically for targeting hematopoeitic stem cells), and PEG-modified liposomes. However, the cited section of McSwiggen does not describe an siRNA gene (as opposed to the siRNA itself) complexed to anything. Moreover, while the liposomes that are hypothesized for administration include PEG modified liposomes and immuno-liposomes, there is no discussion of a liposome that, for example, is both PEG modified (as in a conjugation agent) and that also comprises an antibody. Furthermore, there is simply no discussion at all of an antibody conjugated to the liposome that targets the relevant liposome to a *receptor* on a cell.

With respect to the rejection's argument regarding inherency of these and other features of the invention (Action at page 13), the Examiner is respectfully reminded that, in order for a disclosure to be inherent, the missing descriptive matter must (1)

necessarily be present in the reference, and (2) be in a form that is recognizable to one of skill. *Continental Can Co. v. Monsanto Co.* 20 (Fed Cir. 1991) USPQ2d 1545 1553 n1. Neither of these requirements can be met in the present case. The rejection offers no reasoning as to *why* the McSwiggen compositions would *necessarily* include those that are claimed, and Applicants can discern no such reason from the passages at issue. Why, for example, would the compositions of McSwiggen *necessarily* include a gene encoding an siRNA, within a PEG-modified liposome that also includes an antibody against a receptor, when this combination of elements is not recited? This question is particularly relevant because many other different combinations of possible elements are recited in the passages at issue (though few, if any of them, appear actually to have been made). Similarly, given that the relevant passages recite many combinations of elements *other* than those claimed, how is one of skill to appreciate an unrecited combination of elements similar to that which is claimed in the subject application?

Applicants respectfully submit that there is no teaching, inherent or express, of the claimed composition. The passages at issue in McSwiggen simply recite a laundry list of possibilities that do not actually include Applicants' claimed composition within them. The rejection should, therefore, be withdrawn.

THE CLAIMS ARE NOT OBVIOUS

Claims 1-17 were rejected for alleged obviousness over Zhang (2002), Shi et al. (2001) and Paddision et al. (2002). Applicants respectfully traverse.

As an initial matter when setting forth a *prima facie* case for obviousness, the Office must establish how the combination of references discloses all of the limitations of any rejected claim. MPEP 2143. The combination of references fails this basic test for obviousness.

In particular, Zhang (2002) is interpreted as including a gene that encodes an shRNA. Action at page 16. This is incorrect. Zhang (2002) relates to a completely different technology. Zhang (2002) demonstrates that the delivery of an expression plasmid *encoding a 700 nucleotide (nt) antisense RNA* against the human EGFR with receptor-targeted nanocontainers has a 100% increase in survival in mice with intra-cranial brain cancer. This *antisense* RNA is not an shRNA, nor does it encode such an

shRNA. Indeed, an example shRNA described in the application is <5% the size of the 700 nt antisense RNA used by Zhang (2002) and has a completely different mechanism of action. One would have had no way of knowing whether results similar to Zhang et al. (2002) could be achieved using an shRNA.

Briefly, shRNA is processed and acts in a cell using a different mechanism of action (RNA interference) as compared to a classical anti-sense RNA molecule. To achieve RNAi from an expressed plasmid RNA requires action of cell enzymes (e.g., Dicer) to produce the shRNA, and the action of the shRNA on mRNA leads to specific cleavage of the mRNA, rather than translation inhibition by RNAse H cleavage as may occur in anti-sense inhibition. Thus, there is simply no way of equating anti-sense and shRNA technologies. Indeed, prior to the present application, there had been multiple demonstrations of antisense gene therapeutic effects on cancers, similar to Zhang (2002); *however, there was not a single previous demonstration of an increase in survival from cancer of any type with intravenous shRNAi gene therapy, such as described in the specification* (see specification figure 2). The present application represents a pioneering invention in this respect.

The combination of Shi (2001) and Paddison (2002) with Zhang (2002) do nothing to provide elements of the invention absent from Zhang (2002), e.g., as discussed above. Shi et al. (2001) does not describe compositions for the inhibition of gene expression at all, but, rather, *expression* of a reporter gene in the brain (Shi (2001) does not relate to RNAi or even to anti-sense technology). Paddison (2002) relates to compositions for *in vitro* delivery of shRNA, using delivery vehicles (cationic liposomes) that are entirely unrelated to the compositions of the present invention. Cationic liposomes as taught in Paddison (2002) are microparticle aggregates of an anionic DNA and the cationic lipid. Such microparticles aggregate in saline, which triggers uptake by cells in culture via phagocytosis. However, these aggregates are immediately embolized in the lung *in vivo*, which is why cationic liposomes, i.e., the delivery systems employed by Paddison (2002), cannot beneficially be used *in vivo*. In any case, the Paddison (2002) compositions are simply unrelated to the claimed invention.

Furthermore, the rejection is also fatally defective in establishing a *prima facie* case of obviousness because it neither establishes a motivation to combine the references as proposed in the rejection, nor any expectation that such a combination would be successful, as also required. MPEP 2143.

With respect to motivation to combine, nothing in the art itself suggests the particular combination of references made by the rejection. At most, the rejection is an impermissible hindsight reconstruction of features of completely different systems and compositions in an attempt to pick and choose features to provide Applicants' claimed compositions. In essence, the rejection attempts to combine an in vitro model system (Paddison 2002) relating to cationic liposomes and having no in vivo applicability for the reasons already noted, with an in vivo reference (Zhang 2002), pulling arbitrarily selected features of the very different compositions of these references together in an attempt to provide the claimed invention. Shi et al (2001) has no clear relevance to the claimed invention, i.e., adds nothing to Zhang 2002 or Paddison (2002). The rejection simply does not establish any particular motivation, drawn from the references or the art itself, rather than from a raw hindsight reconstruction of Applicants' invention, to combine the references in the manner suggested.

Moreover, as already noted, absent Applicants' invention, there was simply no way of knowing whether Applicants' shRNA gene composition would work. Applicants provided the first ever demonstration of shRNA inhibition of gene expression *in vivo* in an animal using their new composition; absent Applicants' pioneering results, there was no expectation that Applicants' composition would have such an activity.

Accordingly, the combination of references fails all three criteria for establishing a case of obviousness, i.e., the combination of elements does not provide the limitations of the rejected claims, there is no specific motivation that can be drawn from the art for combining the references and there would have been no expectation, absent Applicants' pioneering results, that the proposed combination would be successful. Accordingly, the rejection must be withdrawn.

THE CLAIMS MEET THE WRITTEN DESCRIPTION REQUIRMENT

Claims 1-17 were rejected for alleged failure to meet the written description requirement. Applicants traverse.

The rejection alleges that the genus of, e.g., claim 1 uses the term "gene" which can comprise any of a variety of different elements (promoters, enhancers, introns, exons, etc.). The rejection further argues that "the claimed 'gene' can be any gene that comprises sufficient genetic information to encode an shRNA and has not disclosed any distinguishing characteristics of the broad genus of claimed genes that would indicate that Applicant was in possession of what is now claimed." Action at page 7. The rejection further argues that no definition of an RNA gene was found in the online medical dictionary, and argues that a gene is a nucleotide that encodes a polypeptide.

Taking the last point first, Applicants respectfully note that terminology in the application is ubiquitous to the technology at issue. The Examiner is referred to Eddy (2001) "Non Coding RNA Genes and the Modern RNA World" Nature Reviews (2):919-929. As noted in the review "Non-coding RNA (ncRNA) genes produce functional RNA molecules rather than encoding proteins." Page 9191, Abstract, first sentence. Accordingly, the rejection's argument that all genes encode proteins is outdated and does not reflect the current state of the technology at issue. In fact, it has been understood for decades that many genes encode functional RNAs rather than proteins.

The argument that genes can include any of a variety of known elements (promoters, enhancers, etc.) and that, therefore, one of skill would not know what elements make up genes encoding shRNA also presents rather tortured logic. Applicants do not deny that many gene elements are known. In fact, it is fair to say that millions, if not billions of such elements are now known. However, this simply reflects the advanced state of the art, and obviously makes it *far easier* for one of skill to select appropriate gene elements to achieve desired expression and replication of the shRNA. All one of skill needs to do in constructing a gene of the invention is to select an appropriate expression cassette using known and available genetic elements and to insert an shRNA into the cassette for expression. Nothing more is needed for one of skill to fully appreciate the *structure* of the genus at issue. Nevertheless, to expedite prosecution,

Applicants have simplified the relevant claim language to indicate that the claimed composition includes a gene that encodes an shRNA, rather than having genetic information sufficient to encode the shRNA.

Finally, contrary to the rejection's assertion that only a single species was provided in the application, at least four separate past-tense working examples are described just in Table 2 (Plasmids 964, 966, 967, and 968; all of which were shown to be active). Applicants have, therefore, provided a number of actual working examples of shRNA genes in their disclosures, as well as demonstrating, for the first time, that compositions of the invention show a therapeutic effect *in vivo*. This is a profound breakthrough for molecular medicine and Applicants are entitled to broad scope for their pioneering invention. The rejection must be withdrawn.

THE CLAIMS SHARE UNITY OF INVENTION

Claims 1-32 were restricted into two groups, i.e., claims 1-17 and claims 18-32. Claims 2 and 19 were further subject to a *rejection* of the claims as an allegedly improper *Markush*-style claim ("lack of unity"). Applicants clarify that they have no objection to the *restriction* of claims 1-32 into two groups (claims 1-17 and 18-32) for examination. However, they *traverse* the *rejection* of claims 2 and 19 for allegedly comprising an improper *Markush* group (i.e., traverse the *rejection* for alleged "lack of unity"). Applicants note that the provisions of 818.03(c) do *not* apply to a *rejection* for improper *Markush*, i.e., that all such rejections are *appealable* and not merely addressable by petition. *See also, In Re Weber, Soder and Boksay* 198 USPQ 328, 331 (C.C.P.A. 1978). *See also, In Re Haas* 179 USPQ 623, 624, 625 (*In Re Haas I*) (C.C.P.A. 1973) *In Re Haas* 198 USPQ 334-337 (*In Re Haas II*) (C.C.P.A. 1978) and *In Re Harnisch* 206USPQ2d 1059 (CCPA 1980).

The alleged restriction "groups" at issue in claims 2 and 19 comprise *Markush*-style claim elements for shRNA to particular oncogenic RNAs (EGF, EGFR, HER2, etc.). Because MPEP 803.02 seems at first glance to consider restriction practice of Markush style claims with respect to Unity of Invention (MPEP 803.02), a great deal of confusion has, unfortunately, become commonplace in the Office as to appropriate *restriction* practice when considering questions of restriction practice for *Markush*-style

claims. It is instructive to consider how this section arose in the MPEP to understand what the law is and what it is not when performing this analysis.

After the *Weber* cases, noted above, a previous version of 803.02 that purported to fashion a rejection for "misjoinder" of a Markush-style claim pursuant to the divisional statute (35 USC § 121) was actually *cancelled out of the MPEP*. That is, for a time, the section corresponding to MPEP 803.02 simply stated:

> the subject matter formerly under this subtitle has been cancelled in view of the decisions In Re Weber et al. 198 USPQ 328 (CCPA 1978) and In Re Haas 198 USPQ 334 (CCPA 1978).

Thus, the Office realized that there is a per se prohibition against fashioning misjoinder-style restriction rejections brought under 35 USC § 121—it was plainly well understood that *Weber* and *Haas* categorically and unequivocally forbade the Office from making such "restriction rejections." In 1980, the Courts again considered the issue of "misjoinder" in the seminal case of *In Re Harnisch* 206USPQ2d 1059, which considered whether there was a *non-statutory* basis for a rejection for "lack of unity" *that was entirely distinct from restriction practice authorized by 35 USC 121.* The *Harnisch* Court was plainly concerned that the two issues would be confused, noting that:

> It should be clear from what we have said that we adhere to our holdings in In re Weber, supra and In Re Haas (Haas II), supra. Nothing we have said herein is intended to change or modify them in any way; nor do we think anything said could be construed to have such an effect. The "unity of invention" concept is not to be confused with the "misjoinder" under 35 USC 121 rejection employed in In re Weber. <u>In Weber, we dealt with the use of 35 USC 121, which deals only with restriction requirements, to support the rejection of a single claim. Here we are concerned only with the rejection of a single claim on the distinct ground that it is directed to an improper Markush group.</u>"

The Court's concern that the Patent Office would confuse the issues of divisional practice under 35 USC § 121 and non-statutory unity of invention considerations has, unfortunately, proven to be well founded. In reinstating MPEP § 803.02, the organizers of the MPEP addressed *Harnisch* (it is the Court decision that now underlies the section), but awkwardly left the original previously cancelled headings for

the section in place, seeming to suggest that the issue is really one of restriction practice. As the Court plainly and expressly made clear (*see above*), it is not.

Indeed, as the *Harnisch* court made as clear as possible, the issue when considering "improper Markush" is not an issue of restriction practice at all. Instead, the as the court stated, the possibility that a Markush-style claim may lack of unity of invention, is a *"distinct ground"* of *rejection*, i.e., it is not an issue of restriction practice at all. *Id.*

Indeed, even the Board decision that the Harnisch case was an appeal from had previously reversed the "improper Markush" rejection by the Examiner, which had been based upon 35 USC § 121 (*Haas* and *Weber*, discussed above, plainly required this result), and fashioned a *different* "improper Markush" rejection based upon "unity of invention," an issue gleaned not from statute, but from consideration of judicial precedent (Harnisch at 304-305). The *Harnisch* Court acknowledged the *possibility* of such a "unity of invention" style improper Markush *rejection* under various court precedent (but *not* under any statute and, as specifically noted by the Court, not under 35 USC §121), but found that a rejection was proper *only* where the members of the Markush group were "truly independent *and* distinct." *Id.* at 306, *emphasis in the original.* The Court made quite plain that this was a high hurdle and that the Office had *not* shown a lack of unity in the relevant case, because the subject Markush members at issue could be classified together in a manner that was not "repugnant to scientific coclassification." *Id.* at 305. This is precisely true in the present case as well, i.e., the mRNAs at issue are all oncogenes and are, thus, certainly not "repugnant to scientific coclassification."

Because the unity *rejection* is improper for the reasons noted, it must be withdrawn. Applicants note that MPEP 803.02 provides an appropriate procedure for *species election*, whereby the Examiner may require selection of a representative species for initial examination. Applicants have no objection to the use of this procedure with respect to the *Markush* species of claims 2 and 19 and maintain their election of EGFR.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance

is respectfully requested. If the claims are deemed not to be in condition for allowance after consideration of this Response, *a telephone interview with the Examiner is hereby requested.* Please telephone the undersigned at (510) 337-7871 to schedule an interview.

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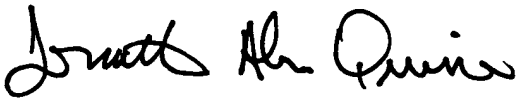
Respectfully submitted,



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Attachments:

1) References: Eddy (2001) "Non Coding RNA Genes and the Modern RNA World" Nature Reviews (2):919-929; Light and Olson (1990) "Transmembrane Movement of Heme" J. Biol. Chem. 265:15623-15631; Uc, A. et al (2004): Heme transport exhibits polarity in Caco-2 cells: evidence for an active and membrane protein-mediated process. Am. J. Physiol. 287: G1150-G1157.
2) A Replacement Sequence Listing with Statement;
3) A declaration pursuant to 37 CFR 1.132 (Katz declaration);
4) A transmittal sheet; and
5) A receipt indication postcard.